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(54) **Crystalline raloxifene hydrochloride**

(57) 6-Hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride is obtained in a novel non-solvated, crystalline form.

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NOVEL PHARMACEUTICAL PRODUCT

This invention is directed to a novel pharmaceutical product. More particularly, the invention is directed to a novel, non-solvated, crystalline form of a 2-aryl-6-hydroxy-3-[4-(2-aminoethoxy)benzoyl]benzo[b]thiophene.

U.S. Patent No. 4,418,068 describes 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride, known as raloxifene hydrochloride, which has shown particular promise as a pharmaceutically-active agent. Unfortunately, this compound has proven extremely difficult to purify. Particular problems have arisen due to solvent contamination. For instance, the process described in the *Journal of Medicinal Chemistry*, 27(8), 1057-1066 (1984), for synthesizing raloxifene suffered from the serious shortcoming that it produced a solvated compound contaminated with chlorobenzene, a known carcinogen. Further, other processes described in the literature utilized a classical aluminum chloride-catalyzed Friedel-Crafts acylation. The product of these processes contain aluminum contaminants and various thioester by-products, which are difficult to remove. Also, the product of these literature processes has an unpleasant residual thiol or sulfide odor.

In accordance with the present invention, the Applicants have now discovered that a novel, non-solvated crystalline form of raloxifene can be produced, free of, for example, chlorobenzene and aluminum contaminants, by the use of a hitherto unknown synthetic process.

The novel crystal form of the invention exhibits substantially the X-ray diffraction pattern shown in Table 1.

Table 1. X-ray Diffraction Pattern for Non-solvated Crystal Form.

	d-line spacing (Angstroms)	I/I ₀ (x100)
5	13.3864	71.31
	9.3598	33.16
	8.4625	2.08
	7.3888	7.57
10	6.9907	5.80
	6.6346	51.04
	6.1717	29.57
	5.9975	5.67
	5.9135	9.87
15	5.6467	38.47
	5.4773	10.54
	5.2994	4.74
	4.8680	4.03
	4.7910	5.98
20	4.6614	57.50
	4.5052	5.75
	4.3701	9.03
	4.2516	69.99
	4.2059	57.64
25	4.1740	65.07
	4.0819	12.44
	3.9673	22.53
	3.9318	100.00
	3.8775	9.07
30	3.7096	33.38
	3.6561	21.65
	3.5576	3.36
	3.5037	7.97
	3.4522	18.02

	d-line spacing (Angstroms)	I/I ₀ (x100)
	3.4138	4.65
	3.2738	10.23
5	3.1857	8.90
	3.1333	6.24
	3.0831	9.43
	3.0025	12.13
	2.9437	4.96
10	2.8642	7.70
	2.7904	11.95
	2.7246	3.05
	2.6652	3.32
	2.5882	7.30

15

Preferably, in the new, non-solvated form of raloxifene hydrochloride, the amount of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride present in the crystalline material is at least 95% by weight (w/w), preferably at least 98%, more preferably at least 99%. More particularly, this preferred form is substantially free from chlorobenzene. Further, this preferred form is also substantially free from aluminum salts or organoaluminum impurities. Also, this preferred form is substantially odor free.

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The term "substantially free from chlorobenzene", as used herein in reference to the non-solvated crystalline 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride, represents a compound containing less than 5% of chlorobenzene calculated on a weight basis (w/w). Preferably, the amount of chlorobenzene is less than 2%, more preferably less than 1%. Most preferably, the amount of chlorobenzene in the non-solvated crystalline material is less than 0.6%.

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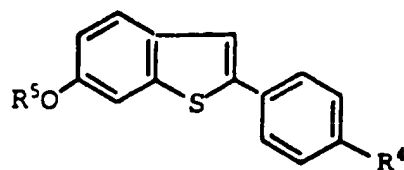
The term "substantially free from aluminum salts or organoaluminum impurities", as used herein in reference to the non-solvated crystalline 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride, represents a crystalline compound containing less than 5% of aluminum salts or organoaluminum impurities calculated on a weight basis (w/w). Representative aluminum salts include, but are not limited to, aluminum hydroxide, aluminum oxides, and hydrated forms thereof. Representative organoaluminum impurities include, but are not limited to, aluminum alkoxides, aluminum(III) complexed to the formula I or IV compounds, and thioaluminates. Preferably, the amount of aluminum salts or organoaluminum impurities is less than 2%, more preferably less than 1%.

The term "substantially odor free", as used herein in reference to the non-solvated crystalline 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride, represents a compound containing less than 3% of mercaptan or sulfide impurities. Preferably, the amount of mercaptan or sulfide impurities is less than 2%, more preferably less than 1%. Representative mercaptan or sulfide impurities include, but are not limited to, C₁-C₆ alkylthiols and methyl C₁-C₆ alkyl sulfides.

This non-solvated crystalline material is more pure than the material produced by the processes described in the literature. The present material is free of aluminum impurities, as well as, chlorinated aliphatic hydrocarbon solvents and aromatic solvents. This non-solvated crystalline form is particularly preferred for use in the manufacture of pharmaceutical compositions.

Preparation of this new crystalline form of raloxifene hydrochloride required the discovery of a new process which comprised the steps of:

(a) acylating the benzothiophene of the formula



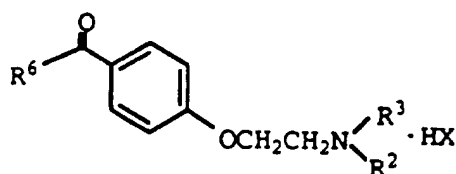
II

wherein:

R⁴ is C₁-C₄ alkoxy, and

R⁵ is C₁-C₄ alkyl,

with an acylating agent of the formula



III

wherein:

R⁶ is chloro, bromo, or hydroxyl,

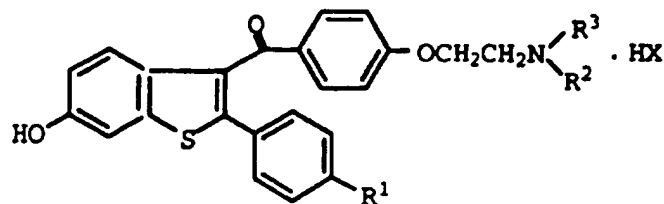
HX is HCl or HBr; and

R² and R³ together with the adjacent nitrogen atom form a piperidino group;

in the presence of BX₃', wherein X' is chloro or bromo;

(b) dealkylating the phenolic groups of the acylation product of step (a) by reacting with additional BX₃', wherein X' is as defined above;

(c) isolating a crystalline solvate of a compound of the formula



I

wherein

R¹ is hydroxyl; and

HX, R², and R³ are as defined above;

(d) reacting said crystalline solvate in methanol, or in a mixture of methanol and water, with about one equivalent of base,

5 (e) optionally extracting the solution from step (d) with an aliphatic hydrocarbon solvent,

(f) adding about one equivalent of hydrochloric acid to the methanolic solution from step (d) or (e), and

(g) isolating the non-solvated crystalline compound.

10 In the above-described process it is preferred that the variables are as follows: R^4 is methoxy, R^5 is methyl, R^6 is chloro, HX is HCl , BX'_3 is BCl_3 , the aliphatic hydrocarbon solvent is hexane or heptane, and the base is sodium hydroxide.

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The term "molar equivalents", as used herein, refers to the number of moles of the boron trihalide reagent in relation to the number of moles of the starting benzo-
thiophene compound. For example, three millimoles of boron
20 trichloride reacted with one millimole of the benzothiophene compound would represent three molar equivalents of boron trichloride.

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The term "solvate" represents an aggregate that comprises one or more molecules of the solute, such as a formula I compound, with a molecule of solvent. Representative solvates are formed with chlorobenzene and 1,2-dichloroethane.

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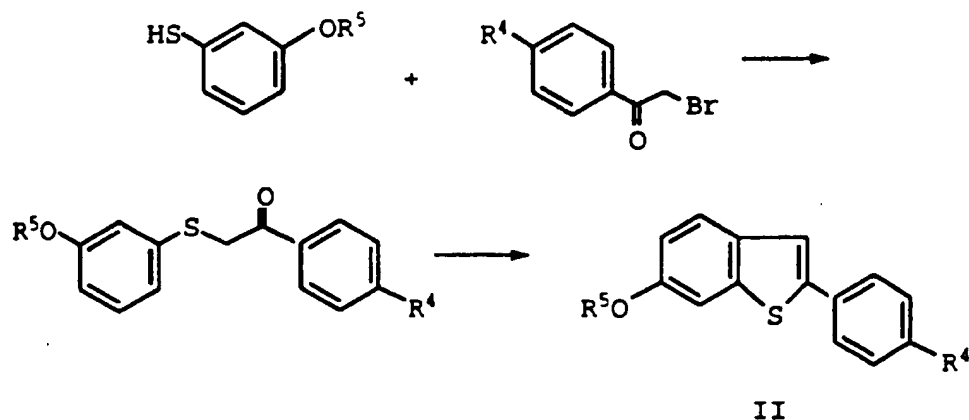
The new process used to prepare the novel crystal form of the present invention uses boron tribromide or boron trichloride as the acylation catalyst in place of the aluminum chloride described in the literature processes for preparing raloxifene. Aluminum chloride is difficult to
35 handle, especially on a commercial scale. Also, a large amount of aluminum chloride, typically six equivalents, is required for acylation and dealkylation. Aluminum chloride

produces a large amount of aluminum by-products, which are entrained during precipitation of the product and subsequently difficult to remove from the pharmaceutically active 2-aryl-6-hydroxy-3-[4-(2-aminoethoxy)-benzoyl]benzo-
5 [b]thiophenes. The aluminum chloride-catalyzed reactions are generally a heterogeneous mixture. The process described above is homogeneous, and the boron by-products are soluble in the work-up solvents. Further, the aluminum chloride-catalyzed dealkylation required the addition of a mercaptan
10 or a sulfide for cleavage of the alkyl aryl ether producing dialkyl sulfides, which exhibit offensive odors. These mercaptans or sulfides are removable by recrystallization; however, this produces a recrystallization solvent with the odorous impurities. The new process eliminates the use of
15 aluminum and the use of odorous mercaptans and sulfides. The art processes produced a high quantity of related substances and high levels of residual aluminum salts in the final product. Representative related substances include 6-hydroxy-2-(4-methoxyphenyl)-3-[4-(2-
20 piperidinoethoxy)benzoyl]benzo[b]thiophene, 2-(4-hydroxyphenyl)-6-methoxy-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene, 6-hydroxy-3-(4-hydroxybenzoyl)-2-(4-hydroxyphenyl)benzo[b]thiophene, propyl 4-(2-piperidinoethoxy)thiobenzoate, methyl 4-(2-piperidinoethoxy)benzoate,
25 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)-benzoyl]-5-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene, and 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)-benzoyl]-7-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene. The boron by-products are easily removed from the final
30 product. Also, the new process avoids the disposal of aluminum waste. When the reaction is carried out in 1,2-dichloroethane, the reactions are homogeneous allowing the use of higher concentrations, and produce crystalline solvates that are readily isolated.

35 The Formula II and III compounds, the starting materials for the present invention, can be prepared using standard

synthetic organic methods. The Formula II starting compound can be readily obtained by a synthesis which is exemplified below in Preparation I and outlined in Scheme I.

5 **Scheme I**



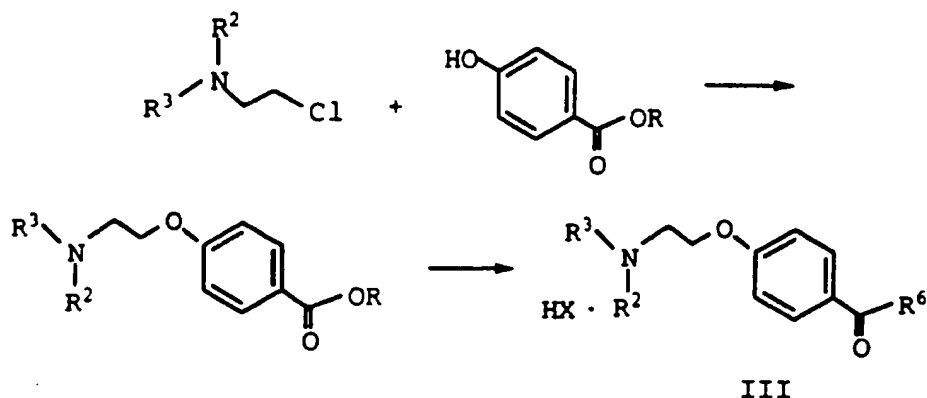
10 The Formula II compounds, wherein R^4 is C_1 - C_4 alkoxy and R^5 is C_1 - C_4 alkyl, can be prepared by first reacting a 3-alkoxybenzenethiol with a 4'-alkoxyphenacyl bromide in the presence of a strong base. Suitable bases for this transformation include, but are not limited to, potassium hydroxide and sodium hydroxide. The reaction is typically carried out in ethanol or a mixture of water and ethanol at a temperature of about 0°C to about 50°C . The next step is cyclization of the 3-alkoxyphenyl phenacyl sulfide. The cyclization is conveniently carried out by heating the 3-alkoxyphenyl phenacyl sulfide in polyphosphoric acid. The cyclization is typically carried out at a temperature of about 80°C to about 120°C , preferably between 85°C and 90°C . The Formula II benzothiophene is typically purified by recrystallization. For example, when R^4 is methoxy and R^5 is methyl, the formula II compound may be recrystallized from ethyl acetate.

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The acylating agent for the present process, a Formula III compound, can be prepared as shown in Scheme II, wherein

the variables R^2 , R^3 , R^6 , and HX are as defined above and R is C_1 - C_4 alkyl.

Scheme II



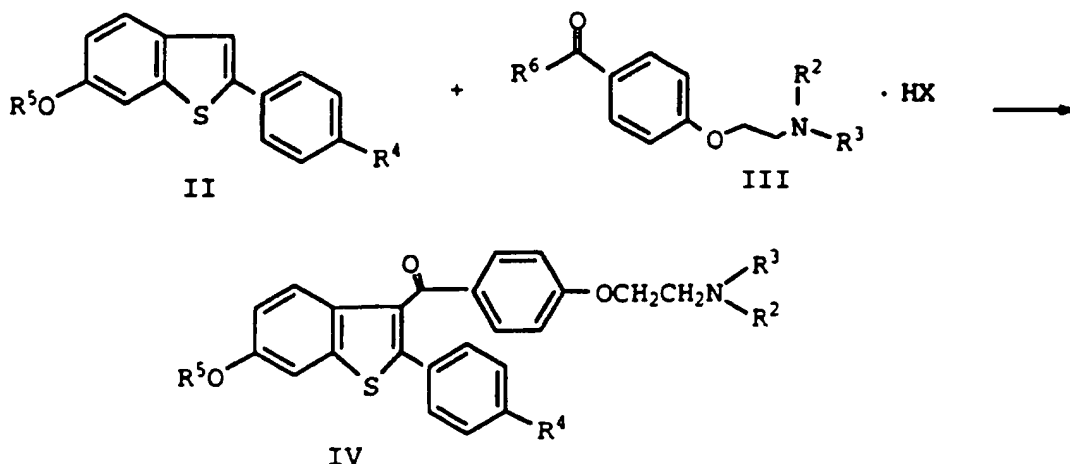
Generally, a C_1 - C_4 alkyl 4-hydroxybenzoate is alkylated with 1-(2-chloroethyl)piperidine in the presence of an inorganic base and the ester group hydrolyzed to produce the Formula III compounds, wherein R^6 is hydroxyl. Suitable inorganic bases for this alkylation include potassium carbonate and sodium carbonate. Suitable solvents for this alkylation are non-reactive polar organic solvents such as methyl ethyl ketone and dimethylformamide. The ester is hydrolyzed using standard synthetic methods, such as by reaction of the alkylated intermediate with an aqueous acid or base. For example, the ethyl ester is readily hydrolyzed by reaction with 5N sodium hydroxide in a water-miscible organic solvent, such as methanol. Acidification of the reaction with concentrated hydrochloric acid produces the Formula III compound, wherein R^6 is hydroxyl, as the hydrochloride salt.

The Formula III compounds, wherein R^6 is chloro or bromo, can be prepared by halogenating the Formula III compounds wherein R^6 is hydroxyl. Suitable halogenating agents include oxalyl chloride, thionyl chloride, thionyl bromide, phosphorous tribromide, triphosgene, and phosgene.

Preferably, R⁶ is chloro. Suitable solvents for this reaction include methylene chloride, 1,2-dichlorobenzene, chlorobenzene, and 1,2-dichloroethane. Preferably, the halogenation reaction is carried out in the same solvent as the subsequent acylation reaction. A catalytic amount of dimethylformamide, from about 0.05 to about 0.25 equivalents, is added to the chlorination reaction. When the reaction is carried out in 1,2-dichloroethane, the reaction is complete after about 2 to 5 hours at about 47°C. The Formula III compounds, wherein R⁶ is chloro, may be stored as a solid, or as a solution or mixture in methylene chloride, chlorobenzene, 1,2-dichlorobenzene, or 1,2-dichloroethane. Preferably, the chlorination reaction and acylation reaction are carried out successively in the same reaction vessel.

The 2-aryl-6-hydroxy-3-[4-(2-aminoethoxy)benzoyl[b]-thiophenes can be prepared by acylation and subsequent dealkylation of the phenolic groups in two distinct steps, or sequentially in a "one-pot" reaction. The step-wise synthesis is described in the following paragraphs. The acylated benzothiophene intermediate, a Formula IV compound, can be prepared as shown in Scheme III, wherein R², R³, R⁴, R⁵, R⁶, and HX are as defined above.

Scheme III

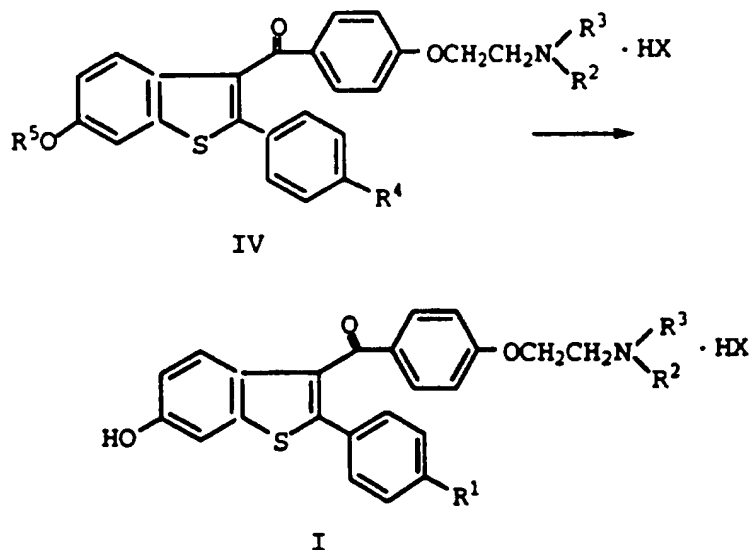


5 Generally, benzothiophene intermediate II is acylated
with a Formula III compound, using boron trichloride or boron
tribromide as the acylation catalyst. The reaction is
carried out in an organic solvent, such as chlorobenzene,
methylene chloride, 1,2-dichloroethane, 1,2-dichlorobenzene,
10 bromobenzene, chloroform, 1,1,2,2-tetrachloroethane, 1,2,3-
trichloropropane, or fluorobenzene. Preferably, the
acylation is carried out in methylene chloride, chloro-
benzene, or 1,2-dichloroethane. Most preferably, the
acylation step is carried out in methylene chloride. The
15 rate of acylation of the Formula II compound and the rate of
dealkylation of the phenolic ethers of the Formula II and IV
compounds varies with the choice of solvent, temperature of
reaction, and choice of boron trihalide. Because the Formula
II compounds having one or more unprotected phenolic groups
20 will not acylate readily under these conditions, the amount
of dealkylation must be minimized. Because boron tribromide
is more preferred for dealkylation of phenolic ethers, the
preferred boron trihalide for catalyzing acylation is boron
trichloride. For boron trichloride-catalyzed reactions in
25 methylene chloride, the acylation reaction can be performed
at room temperature, with minimal dealkylation of the Formula
II and IV compounds. In other solvents, the acylation

reaction is carried out at lower temperatures, such as -10°C to 10°C , to minimize the amount of dealkylation of the reaction starting material and product. When R^6 is chloro, at least 2 molar equivalents of the boron trihalide reagent are required for acylation. When the benzoic acid is used as an acylating agent ($\text{R}^6 = \text{OH}$), five equivalents of the boron trihalide are typically used. The Formula IV compound may be isolated as the hydrochloride or hydrobromide salt, or as the free base.

In the step-wise process, the acylated intermediate (Formula IV compound) is dealkylated to produce the Formula I compound as shown in Scheme IV, wherein R^1 , R^2 , R^3 , R^4 , R^5 , and HX are as defined above.

Scheme IV

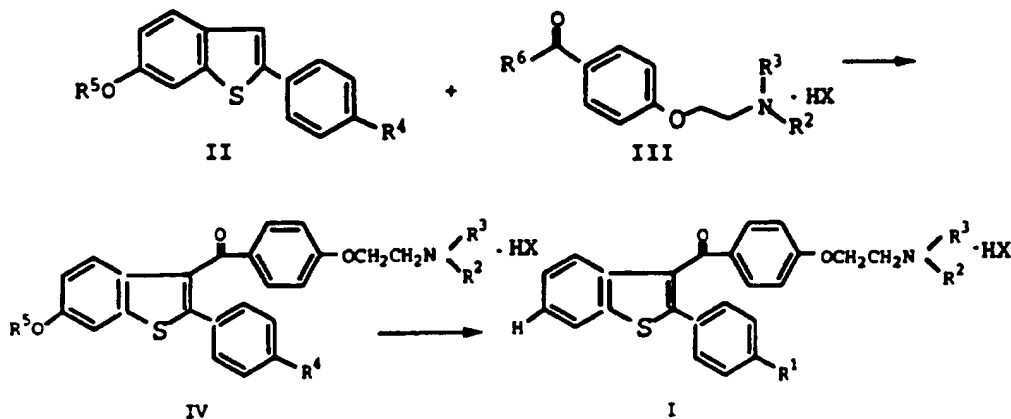


The Formula I compound can be produced by reacting the hydrochloride or hydrobromide salt of the Formula IV compound with boron tribromide or boron trichloride. The preferred boron trihalide for dealkylation is boron tribromide. This dealkylation reaction can be carried out in a variety of organic solvents, such as methylene chloride, 1,2-dichloroethane, chloroform, 1,1,2,2-tetrachloroethane, 1,2,3-

trichloropropane, 1,2-dichlorobenzene, or fluorobenzene. The preferred solvent is 1,2-dichloroethane. When the acid addition salt is used as a starting material, the amount of by-product resulting from dealkylation of the aminoethyl group is minimized. When methylene chloride is used as the solvent and the boron reagent is boron trichloride, the reaction is generally carried out at a temperature of about 55°C to about 75°C, producing the Formula I compound with no detectable cleavage of the aminoethyl group. In other solvents, such as chloroform, 1,2-dichloroethane, 1,2-dichloro-benzene, or fluorobenzene, the dealkylation occurs readily at ambient temperatures. For example, when 1,2-dichloroethane is the solvent, the reaction is generally carried out at 25°C to 35°C with no detectable cleavage of the aminoethyl group. At least four equivalents of the boron trihalide reagent are typically used for complete reaction within a reasonable time.

Preferably, the Formula I compounds are prepared by a "one-pot" synthesis from the Formula II and III compounds as shown in Scheme V, wherein R¹, R², R³, R⁴, R⁵, R⁶, and HX are as defined above.

Scheme V



The benzothiophene Formula II compound is acylated with the Formula III compound in the presence of boron trichloride or boron tribromide; boron trichloride is preferred for the

"one-pot" process. The reaction can be carried out in a variety of organic solvents, such as chloroform, methylene chloride, 1,2-dichloroethane, 1,2,3-dichloropropane, 1,1,2,2-tetrachloroethane, 1,2-dichlorobenzene, or fluorobenzene.

5 The preferred solvent for this synthesis is 1,2-dichloroethane. The reaction is carried out at a temperature of about -10°C to about 25°C, preferably at 0°C. The reaction is best carried out at a concentration of the benzothiophene Formula II compound of about 0.2 M to about

10 1.0 M. The acylation reaction is generally complete after about two hours to about eight hours.

The acylated benzothiophene, the Formula IV compound, is converted to a Formula I compound without isolation. This

15 conversion is performed by adding additional boron trihalide and heating the reaction mixture. Preferably, two to five molar equivalents of boron trichloride are added to the reaction mixture, most preferably three molar equivalents. This reaction is carried out at a temperature of about 25°C

20 to about 40°C, preferably at 35°C. The reaction is generally complete after about 4 to 48 hours. The acylation/dealkylation reaction is quenched with an alcohol or a mixture of alcohols. Suitable alcohols for use in quenching the reaction include methanol, ethanol, and isopropanol.

25 Preferably, the acylation/dealkylation reaction mixture is added to a 95:5 mixture of ethanol and methanol (3A). The 3A ethanol can be at room temperature or heated to reflux, preferably at reflux. When the quench is performed in this manner, the Formula I compound conveniently crystallizes from

30 the resulting alcoholic mixture. Generally, 1.25 - 3.75 mL of alcohol per millimole of the benzothiophene starting material are used.

The crystalline product of this "one-pot" process, when

35 BCl₃ is used, is isolated as the solvate of the hydrochloride salt. These crystalline solvates are obtained under a variety of conditions. Generally, the form of the product of

the present process is determined by choice of acylation/dealkylation solvent, boron trihalide, and work-up conditions. For example, when the acylation/dealkylation solvent is 1,2-dichloroethane, 1,2,3-trichloropropane, or fluorobenzene, the isolated product is the crystalline solvate containing 1,2-dichloroethane, 1,2,3-trichloropropane, or fluorobenzene, respectively.

A particularly useful solvate of the formula I compound is the 1,2-dichloroethane solvate. This solvate is prepared by carrying out the "one-pot" acylation/dealkylation process in 1,2-dichloroethane. When R^1 is hydroxyl, R^2 and R^3 together with the adjacent nitrogen form a piperidino group, and HX is HCl, the 1,2-dichloroethane solvate can exist in two distinct forms. One crystalline solvate form, termed crystal form I, is prepared by quenching the boron trichloride-catalyzed acylation/dealkylation reaction with ethanol. Preferably, a mixture of ethanol and methanol (95:5) is used in the preparation of this crystal form. This particular crystal form is characterized by the X-ray diffraction pattern shown in Table 2.

Table 2. X-ray Diffraction Pattern for Crystal Form I.

d-line spacing (Angstroms)	I/I ₀ (x100)
16.1265	3.80
10.3744	8.63

	d-line spacing (Angstroms)	I/I ₀ (x100)
	8.3746	5.29
	7.9883	36.71
5	7.2701	5.06
	6.5567	70.77
	6.2531	6.79
	5.5616	24.05
	5.3879	100.00
10	5.0471	89.64
	4.7391	85.96
	4.6777	39.36
	4.6332	62.60
	4.5191	77.56
15	4.2867	36.82
	4.2365	41.66
	4.1816	49.60
	4.0900	11.28
	3.9496	11.85
20	3.7869	36.25
	3.7577	56.16
	3.6509	40.62
	3.5751	15.65
	3.5181	21.52
25	3.4964	18.53
	3.4361	33.60
	3.3610	6.21
	3.3115	4.95
	3.2564	7.36
30	3.2002	3.80
	3.1199	15.77
	3.0347	14.84
	2.8744	9.67
	2.8174	10.82
35	2.7363	11.51

The amount of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride present in the crystalline material is about 87.1%, as determined using the high performance liquid chromatography (HPLC) assay described below. The amount of 1,2-dichloroethane present in the crystalline material is about 0.55 molar equivalents, as determined by proton nuclear magnetic resonance spectroscopy.

A large, analytically pure single crystal of the form I 1,2-dichloroethane solvate was prepared for single crystal X-ray analysis. This single crystal was prepared by placing a saturated methanolic solution of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride in an atmosphere saturated with 1,2-dichloroethane (see Example 6). A total of 8419 reflections with 2 θ less than 116° were collected, and used to solve the structure. The X-ray structure clearly shows that the crystalline material is a 1,2-dichloroethane solvate having a 1:2 ratio of solvent to solute molecules. The theoretical X-ray powder diffraction pattern spectrum, calculated from the single crystal X-ray data, is identical to that listed in Table 2, indicating that both solvates are identical.

The new, non-solvated crystalline form of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride provided by the invention is preferred for use in pharmaceutical formulations because of the absence of solvent that could adversely affect the patient. This crystal form can be prepared by recrystallization of the solvated hydro-chloride salt produced by the boron trichloride-catalyzed acylation/dealkylation process described above. Generally, the solvated hydrochloride salt is added to a solution of sodium hydroxide in methanol or a mixture of methanol and water. At least one equivalent of base is used for dissolution and to ensure that the hydrochloride salt is

converted to the free base. Activated carbon is optionally added to the resulting solution to facilitate removal of impurities. The mixture is filtered to remove the activated carbon, if present, and any insoluble impurities. The filtrate is optionally extracted with an aliphatic hydrocarbon solvent, such as hexane or heptane, to remove certain residual solvents used in the acylation/dealkylation reaction. The extraction step is required when the acylation/dealkylation reaction is carried out in aromatic solvents, such as o-dichlorobenzene. The methanol solution is acidified with hydrochloric acid, such as gaseous or aqueous hydro-chloric acid, causing crystallization of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]-thiophene as the non-solvated hydrochloride salt. The resulting crystalline slurry is preferably stirred at ambient temperature for about one to about two hours to ensure complete crystallization. The non-solvated crystalline form is isolated by filtration, followed by drying in vacuo.

The new, non-solvated crystalline form of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride can be prepared by a second recrystallization process from certain solvated forms of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride produced by the BCl_3 -catalyzed acylation/dealkylation process described herein. Generally, the solvated hydrochloride salt is dissolved in a hot solution, from about 50°C to about the reflux temperature, comprising methanol and water, where the water is about three percent to about ten percent by volume. The resulting solution can be filtered to remove insoluble impurities. The solution, or the filtrate, is concentrated by distillation of the solvent, producing the non-solvated crystalline material.

This non-solvated crystalline material is isolated using standard techniques, such as by filtration and drying. This hot methanol/water crystallization process can be used for the preparation of the non-solvated crystal form from certain crystalline solvates, wherein the boiling point of the solvent in the solvate is less than about 85°C.

This second recrystallization process produces the new, non-solvated crystalline form of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride as large rectangular crystals. These crystals are particularly advantageous in production-scale processes for the manufacture of this pharmaceutically-useful compound. For example, the large rectangular crystals facilitate separation and isolation from the recrystallization medium, are easily washed with solvent to remove solvent residues, and are easily handled in the drying process. Using laser light diffraction techniques to estimate the particle size of these large crystals, the average particle size is larger than 100 microns.

The following examples further illustrate the present invention. The examples are not intended to be limiting to the scope of the invention in any respect, and should not be so construed. All acylation and dealkylation experiments were run under positive pressure of dry nitrogen. All solvents and reagents were used as obtained. The percentages are generally calculated on a weight (w/w) basis; except for HPLC solvents which are calculated on a volume (v/v) basis. Proton nuclear magnetic resonance (¹H NMR) spectra were obtained on a Bruker AC-300 FTNMR spectrometer at 300.135 MHz. Melting points were determined by differential scanning calorimetry (DSC) in a TA Instrument DCS 2920 using a closed cell and a heating rate of 2°C/minute. The X-ray powder diffraction spectra were obtained in a Siemens D5000 X-Ray Powder Diffraktometer, using copper radiation and a Si(Li) detector.

The reactions were generally monitored for completion using high performance liquid chromatography (HPLC). The reaction producing the acid chloride, the Formula III compound wherein R⁶ is chloro, was monitored using a Zorbax RX-C8 column, (25 cm x 4.6 mm ID, 5 μ particle) eluting with a mixture of 60 mM phosphate (KH₂PO₄) and 10 mM octane-sulfonate (pH 2.0)/acetonitrile (60:40). The Formula III compound was derivatized with methanol, and analyzed using a methyl ester reference standard. The reaction was monitored by the addition of about 0.3 mL of the acid chloride solution to 1 mL of HPLC grade methanol. The resulting mixture was shaken vigorously and allowed to derivatize. After 30 minutes, acetonitrile (6 mL) was added followed by dilution to 100 mL with the eluent described above.

The acylation, dealkylation, or acylation/dealkylation reactions were also monitored for completion by HPLC. A sample of the reaction mixture was assayed using a Zorbax RX-C8 column (25 cm x 4.6 mm ID, 5 μ particle), eluting with a gradient as shown below:

Gradient Solvent System

	Time (min.)	A (%)	B (%)
25	0	60	40
	5	60	40
	10	45	55
	20	38	62
	25	45	55
30	32	45	55
	37	60	40
	42	60	40

A: 0.05 M HClO₄ (pH=2.0)

B: acetonitrile

The reaction mixture was analyzed by diluting a 0.1 to 0.2 mL sample to 50 mL with a 60:40 mixture of A/B. Similarly, the mother liquor of the recrystallizations was sampled in a similar manner.

The amount (percentages) of 6-hydroxy-2-(4-hydroxy-phenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride in the crystalline material (purity) was determined by the following method. A sample of the crystalline solid (5 mg) was weighed into a 100-mL volumetric flask, and dissolved in a 70/30 (v/v) mixture of 75 mM potassium phosphate buffer (pH 2.0) and acetonitrile. An aliquot of this solution (10 μ L) was assayed by high performance liquid chromatography, using a Zorbax RX-C8 column (25 cm x 4.6 mm ID, 5 μ particle) and UV detection (280 nm). The following gradient solvent system was used:

Gradient Solvent System (Purity)

	Time (min)	A (%)	B (%)
	0	70	30
	12	70	30
	14	25	75
	16	70	30
	25	70	30

A: 75 mM KH_2PO_4 buffer (pH 2.0)

B: acetonitrile

The percentage of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride in the sample was calculated using the peak area, slope (m), and intercept (b) of the calibration curve with the following equation:

$$\% \text{ purity} = \frac{\text{peak area} - b}{m} \times \frac{\text{sample volume (mL)}}{\text{sample weight (mg)}}$$

The amount (percentage) of solvent, such as methanol, ethanol, or 1,2-dichloroethane, present in the crystalline material is determined by gas chromatography. A sample of the crystalline solid (50 mg) was weighed into a 10-mL volumetric flask, and dissolved in a solution of 2-butanol (0.025 mg/mL) in dimethylsulfoxide. A sample of this solution was analyzed on a gas chromatograph using a DB Wax column (30 m x 0.53 mm ID, 1 μ particle), with a column flow of 10 mL/min and flame ionization detection. The column temperature was heated from 35°C to 230°C over a 12 minute period. The amount of solvent was determined by comparison to the internal standard (2-butanol), using the following formula:

$$\% \text{ solvent} = \frac{C}{D} \times \frac{E}{F} \times \frac{G}{H} \times I$$

wherein:

C = ratio of solvent in sample

D = average ratio of standard for specific solvent

E = average weight of standard

F = weight of sample (mg)

G = volume of sample (10 mL)

H = volume of standard (10,000 mL)

I = purity of standard (%)

Preparation 1

6-Methoxy-2-(4-methoxyphenyl)benzo[b]thiophene

A solution of 3-methoxybenzenethiol (100 grams) and potassium hydroxide (39.1 grams) in water (300 mL) was added to denatured ethanol (750 mL), and the resulting mixture cooled to about 0°C. The cold mixture was treated with 4'-methoxyphenacyl bromide (164 grams) in several small portions. Upon complete addition, the mixture was cooled for an additional ten minutes, then allowed to warm to room temperature. After three hours, the mixture was concentrated in vacuo, and the residue treated with water (200 mL). The

resulting mixture was treated with ethyl acetate, and the phases were separated. The organic phase was washed with water (2x), sodium bicarbonate solution (2x), and sodium chloride solution (2x). The organic phase was then dried over magnesium sulfate, filtered, and evaporated to dryness in vacuo to give 202 grams of α -(3-methoxyphenylthio)-4-methoxyacetophenone. This crude product was crystallized from methanol and washed with hexane to give 158 grams. Melting point 53°C.

Polyphosphoric acid (930 grams) was heated to 85°C and treated with the intermediate product from above (124 grams) in small portions over 30 minutes. Upon complete addition, the resulting mixture was stirred at 90°C. After an additional 45 minutes, the reaction mixture was allowed to cool to room temperature. This mixture was treated with crushed ice while the mixture was cooled in an ice bath. The resulting mixture was treated with water (100 mL) producing a light pink precipitate. The precipitate was isolated by filtration, washed with water and methanol, and dried in vacuo at 40°C to give 119 grams of 6-methoxy-2-(4-methoxyphenyl)benzo[b]thiophene. This crude product was slurried in hot methanol, filtered, and washed with cold methanol. The resulting solid material was recrystallized from ethyl acetate (4 liters), filtered, washed with hexane, and dried in vacuo to 68 grams of the title compound. Melting point 187-190.5°C.

Preparation 2

Ethyl 4-(2-Piperidinoethoxy)benzoate

A mixture of ethyl 4-hydroxybenzoate (8.31 g), 1-(2-chloroethyl)piperidine monohydrochloride (10.13 g), potassium carbonate (16.59 g), and methyl ethyl ketone (60 mL) was heated to 80°C. After one hour, the mixture was cooled to about 55°C and treated with additional 1-(2-chloroethyl)-piperidine monohydrochloride (0.92 g). The resulting mixture

was heated to 80°C. The reaction was monitored by thin layer chromatography (TLC), using silica-gel plates and ethyl acetate/acetonitrile/triethylamine (10:6:1, v/v). Additional portions of 1-(2-chloroethyl)piperidine hydrochloride are added until the starting 4-hydroxybenzoate ester is consumed. Upon complete reaction, the reaction mixture was treated with water (60 mL) and allowed to cool to room temperature. The aqueous layer was discarded and the organic layer concentrated in vacuo at 40°C and 40 mm Hg. The resulting oil was used in the next step without further purification.

Preparation 3

4-(2-Piperidinoethoxy)benzoic Acid Hydrochloride

A solution of the compound prepared as described in Preparation 2 (about 13.87 g) in methanol (30 mL) was treated with 5 N sodium hydroxide (15 mL), and heated to 40°C. After 4 1/2 hours, water (40 mL) was added. The resulting mixture was cooled to 5-10°C, and concentrated hydrochloric acid (18 mL) was added slowly. The title compound crystallized during acidification. This crystalline product was collected by filtration, and dried in vacuo at 40-50°C to give 83% yield of the title compound. Melting point 270-271°C.

Preparation 4

4-(2-Piperidinoethoxy)benzoyl Chloride Hydrochloride

A solution of the compound prepared as described in Preparation 3 (30.01 g) and dimethylformamide (2 mL) in methylene chloride (500 mL) was treated with oxalyl chloride (10.5 mL) over a 30-35 minute period. After stirring for about 18 hours, the reaction was assayed for completion by HPLC analysis. Additional oxalyl chloride may be added to the reaction if the starting carboxylic acid is present. Upon completion, the reaction solution was evaporated to dryness in vacuo. The residue was dissolved in methylene chloride (200 mL), and the resulting solution evaporated to

dryness. This dissolution/evaporation procedure was repeated to give the title compound as a solid. The title compound may be stored as a solid or as a 0.2 M solution in methylene chloride (500 mL).

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Example 1

6-Methoxy-2-(4-methoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene Hydrochloride

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A mixture of the compound prepared as described in Preparation 1 (8.46 grams) and the acid chloride prepared as described in Preparation 3 (10.0 grams) in methylene chloride (350 mL) was cooled to about 20-25°C. The cool mixture was treated with boron trichloride (2.6 mL), and the resulting mixture mechanically stirred. The reaction was monitored by HPLC using the assay described above. After 85 minutes, the *in situ* HPLC yield based on a 6-methoxy-2-(4-methoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene standard was 88%.

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Example 2

6-Hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene Hydrochloride

1,2-Dichloroethane Solvate

25

(Crystal Form I)

A solution of 6-methoxy-2-(4-methoxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride (2.0 g) in 1,2-dichloroethane (20 mL) was treated with boron trichloride (2.0 mL). The resulting mixture was stirred at 35°C for about 18 hours. A mixture of ethanol and methanol (10 mL, 95:5, 3A) was treated with the reaction mixture from above, causing the alcoholic mixture to reflux. Upon complete addition, the resulting crystalline slurry was stirred at 25°C. After one hour, the crystalline product was filtered, washed with cold ethanol (10 mL), and dried at 40°C *in vacuo* to give 1.78 g of the title compound. The X-ray

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powder diffraction pattern is identical to that reported in Table 1. Melting point 255°C.

Purity: 80.2%

1,2-Dichloroethane: 7.5% (gas chromatography)

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Example 3

6-Hydroxy-2-(4-hydroxyphenyl)-3-(4-(2-piperidinoethoxy)benzoyl)benzo[b]thiophene Hydrochloride
1,2-Dichloroethane Solvate
(Crystal Form I)

10

A mixture of the compound prepared as described in Preparation 2 (15 g) and dimethylformamide (0.2 mL) in 1,2-dichloroethane (250 mL) was cooled to 0°C. Phosgene (8.25 mL) was condensed in a cold, jacketed addition funnel (-10°C), and added to the cold mixture over a period of two minutes. The resulting mixture was heated to about 47°C. After about two and one half hours, the reaction was assayed by HPLC for completion. Additional phosgene may be added to drive the reaction to completion. Excess phosgene was removed by vacuum distillation at 30-32°C and 105-110 mm Hg.

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After about three to four hours, the reaction solution was treated with the compound prepared as described in Preparation 1 (13.52 g). The resulting solution was cooled to 0°C. Boron trichloride (12.8 mL) was condensed in a graduated cylinder, and added to the cold reaction mixture. After eight hours at 0°C, the reaction solution was treated with additional boron trichloride (12.8 mL). The resulting solution was heated to 30°C. After 15 hours, the reaction was monitored for completion by HPLC.

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A mixture of ethanol and methanol (125 mL, 95:5, 3A) was heated to reflux, and treated with the reaction solution from above over a 60 minute period. Upon complete addition, the acylation/demethylation reaction flask was rinsed with additional ethanol (30 mL). The resulting slurry was allowed

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to cool to room temperature with stirring. After one hour at room temperature, the crystalline product was filtered, washed with ethanol (75 mL), and dried at 40°C in vacuo to give 25.9 g of the title compound. The X-ray powder diffraction pattern is reported in Table 1. Melting point 261°C.

Purity: 87.1%

1,2-Dichloroethane: 0.55 molar equivalents (¹H NMR)

Example 4

6-Hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene Hydrochloride
1,2-Dichloroethane Solvate
(Crystal Form II)

A mixture of the compound prepared as described in Preparation 1 (2.92 g), the compound prepared as described in Preparation 4 (3.45 g), and 1,2-dichloroethane (52 mL) was cooled to about 0°C. Boron trichloride gas was condensed into a cold graduated cylinder (2.8 mL), and added to the cold mixture described above. After eight hours at 0°C, the reaction mixture was treated with additional boron trichloride (2.8 mL). The resulting solution was heated to 35°C. After 16 hours, the reaction was complete.

Methanol (30 mL) was treated with the reaction mixture from above over a 20-minute period, causing the methanol to reflux. The resulting slurry was stirred at 25°C. After one hour, the crystalline product was filtered, washed with cold methanol (8 mL), and dried at 40°C in vacuo to give 5.14 g of the title compound. Because of the difference in work-up condition, the crystalline solvate differs from that obtained in Example 3. Melting point 225°C.

Purity: 86.8%

1,2-Dichloroethane: 6.5% (gas chromatography)

Example 5

6-Hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene Hydrochloride

5 The compound prepared as described in Example 3
(4.0 grams) was slurried in methanol (30 mL) at room
temperature. The resulting mixture was treated with a
solution of sodium hydroxide (0.313 grams) in methanol
(10 mL). After complete dissolution, activated carbon
10 (0.4 grams, Darco G-60, Aldrich Chem. Co., Inc., Milwaukee,
WI) was added to the solution. After 30 minutes, the slurry
was filtered through Whatman #1 filter paper precoated with
diatomaceous earth (Hyflo Super Cel[®], Aldrich Chem. Co.).
The filter cake was rinsed with methanol (10 mL). The
15 combined filtrate was treated (dropwise) with 2N hydrochloric
acid (4 mL). The resulting slurry was stirred for 60 minutes
at room temperature, and filtered. The filter cake was
rinsed with cold methanol (14 mL, 0°C), and dried in vacuo at
60°C for about 18 hours to give 3.00 grams of an off-white
20 free flowing powder. Melting point 262°C. The X-ray powder
diffraction pattern was the same as that shown in Table 1.

Purity: 99.1%

Related substances: 0.85%

Example 6

25 6-Hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)-
benzoyl]benzo[b]thiophene Hydrochloride 1,2-Dichloroethane
Solvate (Crystal Form I)

30 A saturated solution of 6-hydroxy-2-(4-hydroxyphenyl)-3-
[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene hydro-
chloride was produced by stirring a slurry of the compound
prepared as described in Example 5 in methanol at room
temperature overnight. This mixture was filtered (Whatman #1
35 filter paper). A portion of the filtrate (20-25 mL) was
placed in a 50 mL Erlenmeyer flask. This flask was placed
within a glass jar (3.5 in. x 4 in.) containing 1,2-

dichloroethane (about 10 mL). The jar was sealed and the combination was allowed to stand at room temperature. After 24 hours, single crystals had crystallized from the methanol solution. These crystals were filtered and dried *in vacuo*.
5 Melting point 273°C. The crystal structure was determined with a Siemens R3m/V automated four-circle diffractometer using monochromatic copper radiation ($\lambda = 1.54178\text{\AA}$). The crystal structure was solved using the direct methods routine
10 TREF of the SHELXTL PLUS program library. Full-matrix least-squares refinement was conducted with anisotropic temperature factors for all atoms except hydrogens, which were included at calculated positions with isotropic temperature factors. The final R-factor was 8.02%. The crystal data is shown below.

15 **Crystal Data**

Space group	C2/C
Unit cell dimensions	$a = 20.720(7)\text{\AA}$
	$b = 9.492(2)\text{\AA}$
	$c = 28.711(4)\text{\AA}$
	$\beta = 96.50(2)^\circ$
Volume	$5610(2)\text{\AA}^3$
Density (calc.)	1.409 mg/m^3
Absorption coefficient	3.951 mm^{-1}

The X-ray structure clearly shows that the crystalline material is a 1,2-dichloroethane solvate having a 1:2 ratio of molecules of 1,2-dichloroethane to molecules of 6-hydroxy-
30 2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo-
[b]thiophene hydrochloride.

Example 7

6-Hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)-
35 benzoyl]benzo[b]thiophene Hydrochloride

A solution of sodium hydroxide (0.313 g) in methanol

(10 mL) was diluted with additional methanol (50 mL). This solution was treated with the compound prepared as described in Example 4 (4.0 g). After 45 minutes at room temperature, the solution was filtered (Whatman #1 filter paper) and the filter paper rinsed with methanol (3 mL). The filtrate was treated with 2 N hydrochloric acid (4 mL), producing a crystalline slurry. After 1 1/2 hours, this crystalline product was filtered, washed with methanol (5 mL), and dried at 45-50°C in vacuo to give 2.103 g of the title compound. The X-ray powder diffraction pattern was the same as that reported in Table 1. Melting point 261°C.

Purity: 96.5%

Example 8

6-Hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)-benzoyl]benzo[b]thiophene Hydrochloride

A mixture of the compound prepared as described in Example 3 (50g) in methanol (1125mL) and water (60mL) was heated to reflux until dissolution was complete. The hot solution was filtered (Whatman #1 filter paper), and the residue washed with methanol (200mL). The combined filtrate was concentrated by distillation, removing 1207mL of distillate. During the distillation, crystallization occurs. The resulting slurry was allowed to cool to room temperature, and was filtered. The crystalline material was washed with cold (0°C) methanol (170mL). This material was dried in vacuo at 60°C for about 18 hours, with a slight nitrogen purge, to give 38.79g of a tan free flowing solid. The X-ray diffraction pattern was the same as that reported in Table 1. Melting point 275.6°C

Purity: 99.4%

Residual methanol: <0.6% (GC)

Related substances: 0.51% (HPLC)

CLAIMS

1. Non-solvated crystalline 6-hydroxy-2-(4-hydroxy-phenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene
5 hydrochloride exhibiting substantially the following X-ray diffraction pattern obtained with copper radiation:

	d-line spacing (Angstroms)	I/I ₀ (x100)
10	13.3864	71.31
	9.3598	33.16
	8.4625	2.08
	7.3888	7.57
	6.9907	5.80
15	6.6346	51.04
	6.1717	29.57
	5.9975	5.67
	5.9135	9.87
	5.6467	38.47
20	5.4773	10.54
	5.2994	4.74
	4.8680	4.03
	4.7910	5.98
	4.6614	57.50
25	4.5052	5.75
	4.3701	9.03
	4.2516	69.99
	4.2059	57.64
	4.1740	65.07
30	4.0819	12.44
	3.9673	22.53
	3.9318	100.00
	3.8775	9.07
	3.7096	33.38
35	3.6561	21.65

	d-line spacing (Angstroms)	I/I ₀ (x100)
	3.5576	3.36
	3.5037	7.97
5	3.4522	18.02
	3.4138	4.65
	3.2738	10.23
	3.1857	8.90
	3.1333	6.24
10	3.0831	9.43
	3.0025	12.13
	2.9437	4.96
	2.8642	7.70
	2.7904	11.95
15	2.7246	3.05
	2.6652	3.32
	2.5882	7.30

2. The crystalline 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride of Claim 1 wherein the amount of 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride present is at least 95% by weight.

3. The crystalline 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride of any one of Claims 1 and 2 substantially free from chlorobenzene.

4. The crystalline 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride of any one of Claims 1, 2, and 3 substantially free from aluminum salts or organoaluminum impurities.

5. The crystalline 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene hydrochloride of any one of Claims 1-4 substantially odor free.

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6. A pharmaceutical formulation comprising the crystalline compound as claimed in any one of Claims 1 to 5 and one or more pharmaceutically-acceptable carriers, diluents, or excipients.

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7. The crystalline compound as claimed in any one of Claims 1 to 5 for use as a pharmaceutical.

Patents Act 1977
Examiner's report to the Comptroller under Section 17
(The Search report)

Application number
GB 9519028.6

Relevant Technical Fields

- | | |
|--------------------|-------------|
| (i) UK Cl (Ed.N) | C2C(CUK) |
| (ii) Int Cl (Ed.6) | C07D 409/12 |

Search Examiner
P N DAVEY

Date of completion of Search
19 OCTOBER 1995

Databases (see below)

(i) UK Patent Office collections of GB, EP, WO and US patent specifications.

Documents considered relevant following a search in respect of Claims :-
1-7

(ii) ONLINE: CAS ONLINE

Categories of documents

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